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**PATENT**
Attorney Docket No. 067461-5121US
Former Docket No. A-71386-7

# IN THE UNITED STATES PATENT AND TRADEMARK OFFICE BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

*In re* application of:

LAZAR et al.

Serial No. 10/672,280

Filed: September 26, 2003

For: *OPTIMIZED Fc VARIANTS AND METHODS FOR THEIR GENERATION*

Examiner: Chun Wu Dahle

Group No. 1644 Confirmation No.: 8317

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## APPEAL BRIEF

This Brief is filed in support of Appellant's appeal from the Final Rejection of April 13, 2009. A Notice of Appeal was filed on May 28, 2009 with a Pre-Appeal Brief Request for Review. The Notice of Panel Decision from Pre-Appeal Brief Review was mailed August 14, 2009, resulting in a re-set deadline to file the Appeal Brief of September 14, 2009. This Brief is being filed on January 14, 2009, as extended by the accompanying petition for five-month extension.

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## REAL PARTY IN INTEREST

The real party in interest in this appeal is the assignee of record, Xencor, Inc.

## RELATED APPEALS AND INTERFERENCES

No other appeals or interferences are known to Appellants, the undersigned Appellants' representative or the assignee to whom the inventors assigned their rights in the instant case that would directly affect, be directly affected by or bear on the Board's decision in the instant appeal.

## STATUS OF THE CLAIMS

Claims 88-92, 94-112, 135-137 and 139-144 are pending. Claims 90-92, 94-102, 107, 110, 141 and 143 are withdrawn. Claims 1-87, 93, 113-134 and 138 are cancelled. Claims 88, 89, 103-106, 108, 109, 111, 112, 135-137, 139, 140, 142 and 144 are rejected and under appeal.

## STATUS OF THE AMENDMENTS

No amendment to claims has been made or entered after the Final Rejection of April 13, 2009 ("the Final Rejection").

## SUMMARY OF THE CLAIMED SUBJECT MATTER

Claims 88, 89, 90, 91, 92, 96, 97, 103, 135, 136, 139, 140 and 141 are the pending dependent claims. Claims 90-92, 96, 97 and 141 are independent and withdrawn by the Examiner.

Claim 88 is directed to an antibody or immunoadhesin. The antibody or immunoadhesin comprises an amino acid substitution selected from the group consisting of 239D, 239E, 239Q, and 239T, wherein the antibody or immunoadhesin increases binding affinity to an FcγR as compared to its parent antibody or immunoadhesin, and wherein numbering is according to the EU index. This aspect of the invention is described, *inter alia*, in paragraphs [024] to [026] and Table 61.[1]

Claim 89 is directed to an antibody or immunoadhesin. The antibody or immunoadhesin comprises an amino acid substitution selected from the group consisting of 239D, 239E, 239N, 239Q, 239F, 239T, 239H and 239Y, wherein numbering is according to the EU index. This aspect of the invention is described, *inter alia*, in paragraphs [024] to [026] and Table 61.[2]

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[1] See at least variants 86, 89-92, 207, 209, 212, 214, 41, 43, 93-95, 179, 181, 42, 100, 180 and 131.
[2] See at least variants described above and 183, 185-191, 215, 216, 46-48, 182, 184, 101, 102.

Claim 90 is directed to an antibody or immunoadhesin. The antibody or immunoadhesin comprises an amino acid substitution from the group consisting of 239D, 239E, 239Q, and 239T, wherein said antibody or immunoadhesin further comprises an amino acid substitution at a position selected from the group consisting of 234, 235, 240, 241, 243, 244, 245, 247, 256, 262, 263, 264, 265, 266, 267, 269, 270, 290, 296, 297, 298, 299, 312, 313, 322, 325, 326, 327, 328, 329, 330, 331, 332, 333, 334 and 339, wherein said antibody or immunoadhesin increases binding affinity to an FcγR as compared to its parent antibody or immunoadhesin, wherein numbering is according to the EU index. This aspect of the invention is described, *inter alia*, in paragraphs [024] to [026] and Table 61.[3]

Claim 91 is directed to an antibody or immunoadhesin of a parent Fc polypeptide. The antibody or immunoadhesin comprises an amino acid substitution selected from the group consisting of 239D, 239E, 239N, 239Q, 239F, 239T, 239H and 239Y, wherein the antibody or immunoadhesin further comprises an amino acid substitution at a position selected from the group consisting of 234, 235, 240, 241, 243, 244, 245, 247, 256, 262, 263, 264, 265, 266, 267, 269, 270, 290, 296, 297, 298, 299, 312, 313, 322, 325,

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[3] See at least variants 86, 89-92, 207, 209, 212, 214, 41, 43, 93-95, 179, 181, 42, 100, 180 and 131.

326, 327, 328, 329, 330, 331, 332, 333, 334 and 339, wherein numbering is according to the EU index. This aspect of the invention is described, *inter alia*, in paragraphs [024] to [026] and Table 61.[4]

Claim 92 is directed to an antibody or immunoadhesin-of a parent Fc polypeptide. The antibody or immunoadhesin comprises an amino acid substitution selected from the group consisting of 239D, 239E, 239N, 239Q, 239F, 239T, 239H and 239Y, wherein the antibody or immunoadhesin further comprises an amino acid substitution at position 332, wherein numbering is according to the EU index. This aspect of the invention is described, *inter alia*, in paragraphs [024] to [026] and Table 61.[5]

Claim 96 is directed to an antibody or immunoadhesin-of a parent Fc polypeptide. The antibody or immunoadhesin comprises an amino acid substitution at position 239 selected from the group consisting of 239D, 239E, 239Q, and 239T, wherein the antibody or immunoadhesin further comprises an amino acid substitution selected from the group consisting of 234D, 234E, 234N, 234Q, 234T, 234H, 234Y, 234I, 234V, 234F, 235D, 235S, 235N, 235Q, 235T, 235H, 235Y, 235I, 235V, 235F, 240I, 240A, 240T, 240M, 241W, 241L, 241Y, 241E, 241R, 243W, 243L, 243Y, 243R,

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[4] See at least variants described above and 183, 185-191, 215, 216, 46-48, 182, 184, 101, 102.
[5] See at least variants described above and 183, 185-191, 215, 216, 46-48, 182, 184, 101, 102.

243Q, 244H, 245A, 247V, 247G, 262I, 262A, 262T, 262E, 263I, 263A, 263T, 263M, 264L, 264I, 264W, 264T, 264R, 264F, 264M, 264Y, 264E, 265G, 265N, 265Q, 265Y, 265F, 265V, 265I, 265L, 265H, 265T, 266I, 266A, 266T, 266M, 267Q, 267L, 269H, 269Y, 269F, 269R, 296E, 296Q, 296D, 296N, 296S, 296T, 296L, 296I, 296H, 297S, 297D, 297E, 298H, 299I, 299L, 299A, 299S, 299V, 299H, 299F, 299E, 313F, 325Q, 325L, 325I, 325D, 325E, 325A, 325T, 325V, 325H, 327N, 327L, 328M, 328D, 328E, 328N, 328Q, 328F, 328I, 328V, 328T, 328H, 328A, 329F, 330L, 330Y, 330V, 330I, 330F, 330R, 330H, 332D, 332E, 332N, 332Q, 322T, 332H, 332Y, and 332A, wherein numbering is according to the EU index. This aspect of the invention is described, *inter alia*, in paragraphs [024] to [026] and Table 61.[6]

Claim 97 is directed to an antibody or immunoadhesin of a parent Fc polypeptide. The antibody or immunoadhesin comprises an amino acid substitution selected from the group consisting of 239D, 239E, 239N, 239Q, 239F, 239T, 239H and 239Y, wherein the antibody or immunoadhesin further comprises an amino acid substitution selected from the group consisting of 234D, 234E, 234N, 234Q, 234T, 234H, 234Y, 234I, 234V,

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[6] See at least variants 86, 89-92, 207, 209, 212, 214, 41, 43, 93-95, 179, 181, 42, 100, 180 and 131.

234F, 235D, 235S, 235N, 235Q, 235T, 235H, 235Y, 235I, 235V, 235F, 240I, 240A, 240T, 240M, 241W, 241L, 241Y, 241E, 241R, 243W, 243L, 243Y, 243R, 243Q, 244H, 245A, 247V, 247G, 262I, 262A, 262T, 262E, 263I, 263A, 263T, 263M, 264L, 264I, 264W, 264T, 264R, 264F, 264M, 264Y, 264E, 265G, 265N, 265Q, 265Y, 265F, 265V, 265I, 265L, 265H, 265T, 266I, 266A, 266T, 266M, 267Q, 267L, 269H, 269Y, 269F, 269R, 296E, 296Q, 296D, 296N, 296S, 296T, 296L, 296I, 296H, 297S, 297D, 297E, 298H, 299I, 299L, 299A, 299S, 299V, 299H, 299F, 299E, 313F, 325Q, 325L, 325I, 325D, 325E, 325A, 325T, 325V, 325H, 327N, 327L, 328M, 328D, 328E, 328N, 328Q, 328F, 328I, 328V, 328T, 328H, 328A, 329F, 330L, 330Y, 330V, 330I, 330F, 330R, 330H, 332D, 332E, 332N, 332Q, 322T, 332H, 332Y, and 332A, wherein numbering is according to the EU index. This aspect of the invention is described, *inter alia*, in paragraphs [024] to [026] and Table 61.[7]

Claim 103 is directed to an antibody or immunoadhesin of a parent Fc polypeptide. The antibody or immunoadhesin comprises an amino acid substitution selected from the group consisting of 239D, 239E, 239N, 239Q, 239F, and 239T, 239H and 239Y, wherein said antibody or immunoadhesin

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[7] See at least variants described above and 183, 185-191, 215, 216, 46-48, 182, 184, 101, 102.

increases binding affinity to an FcγR as compared to said its parent polypeptide antibody or immunoadhesin, wherein numbering is according to the EU index. This aspect of the invention is described, *inter alia*, in paragraphs [024] to [026] and Table 61.[8]

Claim 135 is directed to an antibody or immunoadhesin comprising a 239D amino acid substitution, wherein said numbering is according to the EU index. This aspect of the invention is described, *inter alia*, in paragraphs [024] to [026] and Table 61, see, for example, variant 86.

Claim 136 is directed to an antibody or immunoadhesin comprising a 239E amino acid substitution, wherein said numbering is according to the EU index. This aspect of the invention is described, *inter alia*, in paragraphs [024] to [026] and Table 61, see, for example, variant 43.

Claim 139 is directed to a protein comprising an Fc variant of a parent Fc polypeptide. The protein comprises an amino acid modification in the Fc region of said parent Fc polypeptide selected from the group consisting of 239D and 239E, wherein the protein increases binding affinity to an FcγR as compared to said parent Fc polypeptide, wherein numbering is according to the EU index. This aspect of the invention is described, *inter alia*, in

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[8] See at least variants described above and 183, 185-191, 215, 216, 46-48, 182, 184, 101, 102.

paragraphs [024] to [026] and Table 61, see, for example, variants 86 and 43.

Claim 140 is directed to a protein comprising an Fc variant of a parent Fc polypeptide. The protein comprises an amino acid modification in the Fc region of said parent Fc polypeptide, selected from the group consisting of 239D and 239E, wherein numbering is according to the EU index. This aspect of the invention is described, *inter alia*, in paragraphs [024] to [026] and Table 61, see, for example, variants 86 and 43.

Claim 141 is directed to a protein comprising an Fc variant of a parent Fc polypeptide. The protein comprises an amino acid modification in the Fc region of the parent Fc polypeptide selected from the group consisting of 239D, 239E, 239N, 239Q, 239F, 239T, 239H and 239Y, wherein said protein further comprises an amino acid substitution at position 332, wherein numbering is according to the EU index. This aspect of the invention is described, *inter alia*, in paragraphs [024] to [026] and Table 61.[9]

[9] See at least variants 41, 42, 89-102, 179-191, 207-210, 212-216.

## GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

Claims 90-92, 94-102, 107, 110, 141 and 143 are withdrawn by the Examiner as allegedly being drawn to a non-elected invention.

Claims 88, 89, 103-106, 108, 109, 111, 112, 135-137, 139, 140, 142 and 144 are allegedly unpatentable under 35 USC 103(a) over Presta (US Patent 6,737,056, filed January 14, 2000, claiming priority to January 15, 1999 and issuing on May 18, 2004).

Claims 88, 89, 103-106, 108, 109, 111, 112, 135-137, 139, 140, 142 and 144 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over the following copending applications:

Claims 1, 2, 10, 13, 17 and 18 of copending USSN 11/124,620,

Claims 9-12 and 19 of copending USSN 11/396,495,

Claims 1-5, 7-13, 20 and 21 of copending USSN 11/538, 406,

Claims 1-5, 8-13, 15, 20 and 21 of copending USSN 11/538,411,

Claims 1, 4-17 and 20-24 of copending USSN 11/544,165,

Claims 1, 3, 5, 6, 9 and 11-13 of copending USSN 11/765,402,

Claims 2, 13-17 and 38 of copending USSN 11/618,457,

Claims 2, 13-17 and 38 of copending USSN 11/618,472,

Claims 2, 13-17 and 38 of copending USSN 11/618,488,

Claims 1, 3, 5, 6, 9 and 11-13 of copending USSN 11/764,001,

Claims 1, 3, 5, 6, 9 and 11-13 of copending USSN 11/765, 353,

Claims 1, 3, 5, 6, 9 and 11-13 of copending USSN 11/765, 390,

Claims 1, 3, 5, 6, 9 and 11-13 of copending USSN 11/765, 402,

Claims 1, 3, 5, 6, 9 and 11-13 of copending USSN 11/766,609.

## ARGUMENT

### *I. Withdrawal of claims as drawn to an allegedly non-elected invention*

Claims 90-92, 94-102, 107, 110, 141 and 143 are withdrawn by the Examiner as allegedly being drawn to a non-elected invention. Appellants argue the withdrawal of 110 and 143 separately from the withdrawal of claims 90-92, 94-102, 107 and 141.

#### A. Restriction and Election of Species Requirement

The original restriction was between Group I directed to polypeptides and Group II directed to methods of treatment. Appellants elected Group I directed to polypeptides.

The Examiner had a further election of species, between

A) an antibody or

B) immunoadhesin.

The Examiner stated that if the antibody species is elected, then the Examiner required a further election of one specific target.

The Examiner further required election of one specific polypeptide species comprising an Fc variant with the following information:

A. specific antibody subtype;

B. a specific substitution in the Fc region with specific amino acid residues; and

C. any functional limitations recited that are encompassed by the elected polypeptide species.

The Examiner also required election of one polypeptide comprising an Fc variant that is:

A. no carbohydrate modification;

B. a glycosylated Fc; or

C. an engineered glycoform.

In response, Appellants elected:

I. An antibody. Appellants noted that all pending claims read on this species.

II. CD20 as the target.

III. With respect to specific polypeptide sequences Appellants elected:

A. IgG1;

B. Position 239 and substitution 239D.

C. Increased affinity for FcγR.

IV. No carbohydrate modification.

Since then, the Examiner extended the search to 239E, 239Q and 239T (see p. 2 of the Final Office Action mailed April 13, 2009).

B. Withdrawal of claims 110 and 143

Claim 110 is drawn to:

An antibody or immunoadhesin according to any of claims 92 and 96-97 wherein said antibody or immunoadhesin further comprises an engineered glycoform.

Claim 143 is drawn to:

A protein according to Claim 139, 140 or 141, wherein said antibody further comprises an engineered glycoform.

Appellants acknowledge that these two claims are drawn to a non-elected invention. However, Appellants note that even if drawn to a non-elected invention, this does not mean the independent claims do not cover variants with engineered glycoforms. In addition, the Appellants have reserved the right to petition for rejoinder under 37 C.F.R. §1.144 should the current claims be held allowable.

C. Withdrawal of claims 90-92, 94-102, 107 and 141

The Appellants strongly contest the withdrawal of these claims. The Examiner states that the dependent claims drawn to amino acid modifications in addition to the elected 239 variants (e.g. claims 90-92, 94-102, 107 and 141) no longer read on the elected species and thus will not be examined.

Currently withdrawn claims 90-92, 94-102, 107 and 141 read on the elected species or species that have been searched; however, the Examiner has withdrawn them as drawn to non-elected invention.

Claims 90-92, 94-102, 107 and 141 all read on the originally elected species. However, the Examiner is now stating that dependent claims to variants **including the original elected species** and further comprising additional limitations will not be examined; thus a claim to the elected species of 239D further comprising an amino acid substitution at an additional different position will not be examined (e.g. claims 90-92, 94-102, 107 and 141).

Under the Examiner's reasoning, all dependent claims are always drawn to a non-elected invention, as by definition, all dependent claims further limit the independent claims. This is clearly erroneous. A dependent claim that reads on the elected species and "further comprises" additional limitations properly reads on the elected species. Examiner is confusing the "election" of a restriction under M.P.E.P. §818 with the election of a species within a Markush claim to facilitate searching under M.P.E.P. §803.02. However, the Examiner is required to examine all claims drawn to the elected invention. The further dependent claims are not "non-elected

species"; these are dependent claims, encompassing all the limitations of the elected species. As such, there is no additional prior art search burden.

For example, under the Examiner's reasoning, a claim reciting an immunoadhesin according to claim 1 further comprising a toxin component would be directed to a "non-elected invention". The Appellants submit that the Examiner's position renders **virtually all** dependent claims, which by definition include further limitations, as directed to a non-elected invention. This is simply not true. As such, they should be examined.

As stated in M.P.E.P. §821.01, the Appellants may traverse an examiner's holding that a given claim is not for elected subject matter. This holding appears to be an appealable rejection (see also Chisum, §12.04[5])[10]. Accordingly, Appellants are in fact appealing the Examiner's holding that claims 90-92, 94-102, 107 and 141 are directed to non-elected subject matter.

The Appellants' position is that assuming the current prior art rejections are overcome, the Examiner must examine the all the dependent claims, including claims 90-92, 94-102, 107 and 141.

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[10] The case law on this point is somewhat unclear, with some courts holding that a determination that a claim is not elected subject matter is a matter for appeal. Other courts suggest that this is petitionable. In an abundance of caution, the Appellants are appealing this decision herein, as well as filing a petition under §1.182.

## *II. Rejection under 35 USC 103(a) over Presta, US Patent 6,737,056*

### A. Claims 88, 90, 98-102 (in part), 103-105, 106-112 (in part), 137, 139, 142-144 (in part)

Claims 88, 90, 98-102 (in part), 103-105, 106-112 (in part), 137, 139, 142-144 (in part) are finally rejected under 35 USC 103(a) over Presta, US Patent 6,737,056.

In the Final Rejection mailed April 13, 2009 the Examiner alleges that Presta:

> teaches that the Fc region of an antibody or immunoadhesin can be altered so that the Fc-related effector functions of the antibody or immunoadhesin can be changed. The scope of the prior art embodiment is not simply limited to what amino acid residues to use to substitute a given pre-existing residue. The key invention of Presta is the identification of positions, e.g. 239 in the Fc region, that interact with the Fc gamma receptors. Presta teaches that S239 is involved in binding of the FcγRs (e.g. see column 3). (emphasis in the Final Office Action).

Appellants respectfully disagree. Although the data in Presta demonstrate that a substitution of alanine (A) at position 239 reduces binding to FcγR, the Examiner relies on the general disclosure of Presta regarding substitutions of any amino acid at any position (referring to the last paragraph on column 19). The Examiner alleges that Presta's teaching "is enabling in the sense that it allows one of ordinary artisan [sic] to make

Fc variants with S239 substituted to any other naturally occurring residues and to select the Fc variants with increased affinity to FcγRs." According to the Examiner, "[a] person of ordinary skill has good reason to pursue the known options, e.g. making S239D (see column 12 and paragraphs between Tables in column 20 of Presta), within his or her technical grasp with reasonable expectation of success." The Examiner concludes that "the claimed S239D, S239E, S239Q and S239T are simply predictable variations."

In addition, the Examiner dismissed the secondary indicia of non-obviousness submitted in the January 13, 2009 response.

As a preliminary matter, Appellants respectfully draw the Board's attention to the Board of Patent Appeal and Interferences' decision in *Ex parte Watkins* (Appeal 2007-2523). Appellants are mindful that *Ex parte Watkins* is a non-binding opinion. However, Appellants believe that in view of the identity of the exact issues in both *Watkins* and the present case, the Board's logic and finding are relevant to the instant application. [11]

In *Watkins*, the independent claim 1 read:

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[11] Appellants note that the Examiner in Watkins is the same Examiner in the present case.

1. A composition comprising a variant of a parent polypeptide having at least a portion of an Fc region, wherein said variant mediates antibody-dependent cell-mediated cytotoxcity (ADCC) in the presence of effector cells more effectively than said parent polypeptide, wherein said variant comprises a histidine, glutamine or tyrosine amino acid at position 280 in the Fc region, and wherein said parent polypeptide is an antibody or immunoadhesin.

In *Watkins,* the Examiner relied on Presta (US Patent No. 6,737,056 (which forms the basis of the present rejections)) "*Presta II*" to reject claim 1 and claims dependent therefrom of under 35 U.S.C. §102(e) as being anticipated by *Presta II.* Specifically, the Examiner based her rejection on the finding that "Presta [II] teaches ... a polypeptide (e.g. antibody or immunoadhesin) comprising a variant Fc region with higher binding affinity to FcγR including FcγRIII and an amino acid substitution at positions such as 280 in the CH2 region for improved antibody –dependent cell-medicate[d] cytotoxicity" and that "Presta [II] defines amino acid residues in a predetermined amino acid sequence with another different amino acid resid[u]e including histidine, glutamine or tyrosine." *Watkins*, at 3. The Examiner also relied on *Ex parte A*, 17 USPQ2d 1716 (BAPAI, 1990) for the rejection.

The Board reversed the rejection. Specifically, the Board rejected the Examiner's reliance on *Presta* II's definition of amino acid substitution which lists twenty standard amino acids, because such definition "does not describe substituting the amino acid at position 280 with any of these twenty amino acids." *Watkins* at 6. Moreover, the Board states:

> [W]e do not agree that Presta [II] provides a specific teaching of substituting the amino acid at position 280 with each of these twenty amino acids and therefore with the three amino acids recited in claim 1. *Id.* at 6.

However, the Examiner bases the instant rejection on the same disclosures of *Presta* relied upon by the Examiner in *Watkins*, and relied on the similar reading of Ex parte A. Thus, identical to *Watkins*, *Presta* does not describe substituting the amino acid at position 239 with any of these twenty amino acids.

The Appellants submit that while *Watkins* is non-precedential, the exact same issue is on appeal here: namely, whether Presta "provides a specific teaching of substituting the amino acid at position [239 in the present appeal] with each of these twenty amino acids and therefore with the [4 or 8] recited in claim 1". As the Board held in *Watkins*, it does not. Accordingly, while the amino acid position is different, the holding in *Watkins* is directly on point with the issue in the present case.

*The teachings of the Presta reference as a whole*

As stated in M.P.E.P. §2141.02 VI., "A prior art reference must be considered in its entirety, i.e. as a whole, including portions that would lead away from the claimed invention." (Emphasis in original).

There are 7 references in the specification that teach that amino acid modifications at position 239 will decrease binding to FcγRs:

1. Of residues 233-239, P238 and S239 have been cited as possibly being involved in binding, but these two residues have never been evaluated by substitution or deletion. See column 3, lines 14-16.
2. In one embodiment, the polypeptide variant with altered FcγR binding activity displays reduced binding to an FcγR and comprises an amino acid modification at any one or more of amino acid positions 238, 239, 248, 249, 252, 254, 265, 268, 269, 270, 272, 278, 289, 292, 293, 294, 295, 296, 298, 301, 303, 322, 324, 327, 329, 333, 335, 338, 340, 373, 376, 382, 388, 389, 414, 416, 419, 434, 435, 437, 438 or 439 of the Fc region, wherein the numbering of the residues in the Fc region is that of the EU index as in Kabat. See column 5, lines 19.
3. The polypeptide variant of interest may display reduced binding to an FcγRIII and comprise an amino acid modification at one or more of amino acid positions 238, 239, 248, 249, 252, 254, 265, 268, 269, 270, 272, 278,

289, 293, 294, 295, 296, 301, 303, 322, 327, 329, 338, 340, 373, 376, 382, 388, 389, 416, 434, 435 or 437 of the Fc region, wherein the numbering of the residues in the Fc region is that of the EU index as in Kabat. (col 5, lines 23-30).

4. The section in Table 2 that recites "reduced binding to both FcγRII and FcγRIII" includes the sole 239 variant made, S239A.

5. To generate an Fc region variant with reduced binding to the FcγR one may introduce an amino acid modification at any one or more of amino acid positions 238, 239, 248, 249, 252, 254, 265, 268, 269, 270, 272, 278, 289, 292, 293, 294, 295, 296, 298, 301, 303, 322, 324, 327, 329, 333, 335, 338, 340, 373, 376, 382, 388, 389, 414, 416, 419, 434, 435, 437, 438 or 439 of the Fc region. (See col 22, lines 55-61).

6. Fc region variants which display reduced binding to FcγRIII include those comprising an Fc region amino acid modification at any one or more of amino acid positions 238, 239, 248, 249, 252, 254, 265, 268, 269, 270, 272, 278, 289, 293, 294, 295, 296, 301, 303, 322, 327, 329, 338, 340, 373, 376, 382, 388, 389, 416, 434, 435 or 437. (Column 23, lines 4-9).

7. Table 6 shows S239A has reduced binding to FcγRII (both FcγRIIA and FcγRIIB) and FcγRIIIA.

The sole reference to "increased binding" with a 239 variant is in claim 13, which **was not part of the application as filed.** The claims as filed have three claims that recite 239: original claim 14 is drawn to altered binding and recites a list of positions including 239; original claim 16 is drawn to reduced binding to an FcγR and recites a list of positions including 239; and original claim 18 is drawn to reduced binding to FcγRII and recites a list of positions including 239. Notably, original claim 23 is drawn to increased binding to an FcγR and does not recite position 239. Thus, the application as filed contains no disclosure of increased binding to any FcγR using a 239 variant.

The first time the concept of increased binding to an FcγR at position 239 was introduced was the amendment dated 12/3/02, when claim 14 changed the preamble from "altered binding" to "increased binding"; the proffered reason stated by the patentee is to conform to the restriction requirement. We note that the Applicants state that "the amendments do not introduce any new matter", a statement with which Appellants clearly take issue.

The fact that this claim was not part of the original disclosure and is the **sole** disclosure relating to increased binding of a 239 variant lessens the strength of this teaching.

Taken together, the 7 references in the specification to **decreased** binding as a result of a change at position 239, weighed against a **single** reference that was not even part of the original disclosure, renders non-obvious claims directed to an antibody or immunoadhesin having increased binding as a result of a substitution at position 239.

Appellants appreciate that "patents are relevant as prior art for all they contain" (see M.P.E.P. §2123). However, in this case, the fact that the sole teaching of increased binding using variants at position 239 was added through a preamble change during prosecution and was not contested does tip the analysis towards a finding that the reference, as a whole, does not render the claimed invention obvious.

In addition, as stated in *Takeda v. Alphapharm*, 492 F.3d 1350, (Fed. Cir. 2007), the factors for evaluation of obviousness are:

> 1) "the scope and content of the prior art"; 2) the "differences between the prior art and the claims"; 3) "the level of ordinary skill in the pertinent art"; and 4) objective evidence of nonobviousness. *KSR*, 127 S.Ct. at 1734 (quoting *Graham*, 383 U.S. at 17-18, 86 S.Ct. 684).

The Court went on to say:

> The KSR Court recognized that "[w]hen there is a design need or market pressure to solve a problem and there are a finite

> number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp." *KSR*, 127 S.Ct. at 1732. In such circumstances, "the fact that a combination was obvious to try might show that it was obvious under § 103." Id. That is not the case here. Rather than identify predictable solutions for antidiabetic treatment, the prior art disclosed a broad selection of compounds any one of which could have been selected as a lead compound for further investigation. Significantly, the closest prior art compound (compound b, the 6-methyl) exhibited negative properties that would have directed one of ordinary skill in the art away from that compound. Thus, this case fails to present the type of situation contemplated by the Court when it stated that an invention may be deemed obvious if it was "obvious to try." The evidence showed that it was not obvious to try. (Emphasis added).

Appellants argue that this is very similar to the situation at hand. The Federal Circuit in *Takeda* started with a discussion of the differences between the prior art and the claims by discussing the selection of a compound as a lead compound. Following this line of reasoning, the first question is whether one of skill in the art would select S239A as a "lead compound" upon which to experiment in order to achieve better Fc$\gamma$R binding. Appellants submit that this is not likely, as S239A had decreased

binding to four of the five tested receptors, with the fifth, FcRn, showing similar binding to wild-type[12].

The Federal Circuit went on to discuss the choice of the claimed compounds and stated:

> The district court found nothing in the prior art to suggest making the specific molecular modifications to compound b that are necessary to achieve the claimed compounds. In reaching that conclusion, the court first found that the process of modifying lead compounds was not routine at the time of the invention. see Page 1350.

Again, Appellants argue the similarity of the present case. There is no motivation to make the specific amino acid modifications claimed in the present case. As shown in *Takeda*, different changes had unpredictable outcomes. Here, the Presta reference itself shows that different amino acid substitutions at the same position render dramatically different results. For example, S267A shows increased binding to both FcγRII and FcγRIII, while S267G essentially eliminates FcγRIII binding. Another example is at position 269: E269A and E269Q both show decreased binding to FcγRIII, while E269D shows unchanged binding to FcγRIII. In addition, some amino

[12] Appellants further note that the lack of a standard deviation number for the binding of S239A to FcRn also brings into question whether this variant actually does have similar binding to wild type.

acid modifications have no effect on binding at all, which is similarly unpredictable. For example, E318A (negatively charged amino acid replaced by small hydrophilic residue) and E318K (negatively charged amino acid replaced by positively charged amino acid residue) both show essentially no change in binding to any FcγR. There are a number of additional examples within Presta to illustrate that this reference directly teaches the unpredictability of making amino acid changes. In view of this, Appellants maintain that the obviousness rejection is in error.

In addition, the Examiner has failed to properly perform the factual inquiry required by the Supreme Court in *KSR Int'l. Co. v. Teleflex Inc.*, 127 S.Ct. 1727 (2007). Thus, it will be shown that the Examiner has failed to establish a *prima facie* case of obviousness under the law of *KSR*.

*The Examiner has failed to properly analyze the Graham factors that form the basis for an obviousness rejection.*

35 USC 103(a) states that

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains.

In *KSR Int'l. Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1734 (2007), the Supreme Court reaffirmed the analysis that it had previously set forth in *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1 (1966), reiterating that "[u]nder § 103, the scope and content of the prior art to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background the obviousness or nonobviousness of the subject matter is determined." The Court stated that "while the sequence of these questions might be reordered in any particular case, the factors continue to define the inquiry that controls." *Id.* Thus, obviousness is a question of law based on underlying facts. *Fromson v. Anitec Printing Plates, Inc.*, 132 F.3d 1437, 1447 (Fed. Cir. 1997). The determination of whether the subject matter as a whole would have been obvious to a person of ordinary skill at the time the invention was made is reviewed by a court for correctness as a matter of law, and the underlying factual determinations are reviewed for clear error. *Id.*

*Level of ordinary skill in the art*

In addition, the Examiner dismissed the secondary indicia of non-obviousness submitted in the January 13, 2009 response. Appellants traverse the rejection.

The Examiner has not provided in the record any indication of the level of ordinary skill in the art. The Examiner's factual inquiry into the *Graham* factors is therefore incomplete at least in this respect. Appellants note that the Federal Circuit has found a person of ordinary skill in the art generally "to be one who thinks along the line of conventional wisdom in the art and is not one who undertakes to innovate, whether by patient, and often expensive, systematic research or by extraordinary insights." *Standard Oil Co. v. American Cyanamid Co.*, 774 F.2d 448 (Fed. Cir. 1985).

*Scope and content of the prior art*

Presta discloses variants of the Fc region of immunoglobulins. In most instances, Presta performs alanine scanning mutagenesis. However, *Presta* does not teach the claimed species position 239 having the required functional limitation. At col. 5, lines 1-4 Presta discloses that a group of modifications that include elected position 239 display "reduced binding to an FcγR." At col. 5, lines 23-25, Presta discloses that a group of modifications that include position 239 display "reduced binding to an FcγRIIIa." The best demonstration of this is in Table 6, which discloses the sole substitution at position 239, which was an alanine substitution, 239A. Table 6 shows that 239A has reduced binding affinity to both FcRIII and FcRII.

*Differences between the prior art and the claims at issue*

As noted previously, claim 88 is directed to an antibody or immunoadhesin that comprises an amino acid substitution selected from the group consisting of 239D, 239E, 239Q, and 239T, wherein the antibody or immunoadhesin increases binding affinity to an FcγR as compared to its parent antibody or immunoadhesin, and wherein numbering is according to the EU index.

In contrast, Presta discloses only a single variant at position 239, an alanine substitution (239A). Importantly, the 239A variant of Presta *reduces* binding to FcγR. That is, Presta does not teach any substitutions at position 239 that enhance binding to an FcγR. Moreover, Presta only teaches one substitution in the specification – an alanine. The only teaching in Presta is that an alanine substitution at position 239 decreases binding to an FcγR.

Thus, in an effort to *increase* binding to an FcγR, one skilled in the art would not be led to substitute D, E, Q or T for the alanine of Presta because alanine decreases binding to an FcγR.

*Combining prior art elements according to known methods to yield predictable results*

Moreover, following the analysis outlined in the M.P.E.P. §2143 and the teachings of the Supreme Court in the KSR case (*KSR v. Telefax*, 82

USPQ2d 1385 (2007)), the teachings of Presta do not render the claimed invention obvious.

The Examiner has repeatedly noted that various substitutions have different effects, and notes the unpredictability of the art (see, for example, Section 9, last paragraph of the Office Action of February 2, 2008). The Examiner cannot on one hand say that the prior art shows unpredictability for the purposes of enablement and simultaneously argue that the prior art is predictable for the purposes of a §103 rejection.

*Simple substitution of one known element for another to obtain predictable results*

The Examiner has pointed to col. 12 to support the position that amino acid substitutions are interchangeable. As outlined above, this exact position by this same Examiner was rejected in the *Ex parte Watkins* (non-precedential) case. Moreover, while Watkins was non-precedential, the Board's analysis is highly germane to the present situation. In *Watkins*, while the basis of the rejection was 102(e), the point made is identical; the Board rejected the Examiner's reliance on *Presta's* definition of amino acid substitution which lists twenty standard amino acids, because such definition "does not describe substituting the amino acid at position 280 with any of these twenty amino acids." *Watkins* at 6. Moreover, the Board states:

> [W]e do not agree that Presta provides a specific teaching of substituting the amino acid at position 280 with each of these twenty amino acids and therefore with the three amino acids recited in claim 1. *Id.* at 6.

Further, Appellants note that alanine is described as hydrophobic. None of the specifically recited substitutions claimed by Appellants are hydrophobic. Therefore one skilled in the art would not be taught to substitute a variant claimed by Appellants. Presta states that the elected substitution is acidic. The 20 amino acids have very different chemical characteristics and cannot be simply substituted one for another. Thus, the teachings in Presta either teach away from the substitution of D (or any of the other amino acids) or alternatively in no way suggest it based on the very different chemical characteristics of naturally occurring S or substituted A.

*Applying a known technique to a known product ready for improvement to yield predictable results*

The comments with respect to item A are equally applicable here. While one skilled in the art is "capable" of performing tests, there has to be a teaching or motivation or suggestion to try certain substitutions. There are none in Presta as Presta does not teach any enhanced variants at position 239.

*Obvious to try*

The comments above are equally applicable here. There is no teaching or motivation to try the substitutions claimed by Applicant because there is only one variant (alanine) and that variant does not enhance binding at position 239. The Examiner states that "a person of ordinary skill in the art has good reason to pursue the known options". However, as required by the KSR Guidelines issued by the Office, the Examiner is required to identify those good reasons. The Examiner does not do so here, nor are there any such reasons.

Some teachings, suggestion or motivation in the prior art that would have lead one of ordinary skill to modify the prior art reference to arrive at the claimed invention

As previously stated, there is no teaching motivation or suggestion in Presta to support this argument. There is no teaching in Presta that would lead one skilled in the art to identify variants at position 239 that enhance binding to the specifically recited substitutions. This is required by KSR and by the KSR guidelines. Again Col. 12 provides no teaching that D would be a good substitution based on the disclosure that A does not enhance binding. There is no teaching there, just a list of 20 amino acids. One skilled in the art is not guided by a list without any suggestions.

Even with the lack of suggestion in Presta one skilled in the art could not have known that D would be a substitution to enhance binding. The only teaching in Presta is that alanine decreases binding. There is no basis for enhanced binding here.

*Secondary Indicia of Non-Obviousness*

As outlined by the Supreme Court in *KSR*, the secondary indicia of non-obviousness is still a relevant factor for consideration in determining non-obviousness. In this case, Appellants would like to point out the commercial success of this Fc technology, including variants at position 239.

Appellants have previously demonstrated that this technology has been licensed by a number of companies, including Genentech, Centocor, MedImmune, Boehringer Ingelheim, Roche, PDL, Chugai and Human Genome Sciences.

In fact, with specific reference to position 239, the Appellants respectfully point out that MedImmune is actually utilizing some of these variants, as evidenced by U.S. Publication No. 2008/0071063, claims 13-16, with specific 239 residues recited, including 239E, 239D, 239Q, 239N, 239F, 239T, 239H and 239Y (claim 14) and 239D (claim 16); Protein Design Labs as evidenced by WO 05102387A2, pages 50 – 51, with 239D, 239E, 239N, 239Q, 239F, 239T, 239H, and 239Y specifically recited at page

50, lines13-14; and Chugai as evidenced by U.S. Publication No. 2007/0087005, claims 3 -5, 9 and 10, with specific 239 residue aspartic acid (D) recited.

In view of the above, Appellants request that the rejection be withdrawn.

B. Claims 89, 91, 92, 94, 95, 96, 97, 98-102 (in part), 106-112 (in part), 135, 136, 140, 141, and 142-144 (in part)

Claims 89, 91, 92, 94, 95, 96, 97, 98-102 (in part), 106-112 (in part), 135, 136, 140, 141, and 142-144 (in part) are finally rejected under 35 USC 103(a) over Presta, US Patent 6,737,056.

The arguments above are incorporated herein by reference. In addition, Appellants maintain that the recited species are patentable over Presta whether or not functional language is recited in the claims. Assuming, *arguendo*[13], that Presta teaches making modifications at position 239, Appellants maintain that the specific 239 variants recited in the claims are not obvious. That is, independent claims 88, 90, 103 and 139 (argued separately above) include the functional limitation that the variants exhibit

[13] Appellants maintain that they do not accept that Presta legitimately teaches making modifications at position 239 to increase binding to an FcγR receptor. However, Appellants acknowledge the existence of claim 13 and thus will argue accordingly, reserving the right to argue this point in this or other cases.

increased binding to an FcγR receptor, while independent claims 89, 91, 92, 96, 97, 135, 136, 140 and 141 do not.

As noted above, as stated in *Takeda v. Alphapharm*, 492 F.3d 1350, (Fed. Cir. 2007), the factors for evaluation of obviousness are:

> 1) "the scope and content of the prior art"; 2) the "differences between the prior art and the claims"; 3) "the level of ordinary skill in the pertinent art"; and 4) objective evidence of nonobviousness. *KSR*, 127 S.Ct. at 1734 (quoting *Graham*, 383 U.S. at 17-18, 86 S.Ct. 684).

The Federal Circuit went on to discuss the choice of the claimed compounds and stated:

> The district court found nothing in the prior art to suggest making the specific molecular modifications to compound b that are necessary to achieve the claimed compounds. In reaching that conclusion, the court first found that the process of modifying lead compounds was not routine at the time of the invention. See page 1350.

Again, Appellants argue the similarity of the present case. There is no motivation to make the specific amino acid modifications claimed in the present case, with or without functional language. As shown in *Takeda*, different changes had unpredictable outcomes. Here, the Presta reference itself shows that different amino acid substitutions at the same position

render dramatically different results. For example, S267A shows increased binding to both FcγRII and FcγRIII, while S267G essentially eliminates FcγRIII binding. Another example is at position 269: E269A and E269Q both show decreased binding to FcγRIII, while E269D shows unchanged binding to FcγRIII. In addition, some amino acid modifications have no effect on binding at all, which is similarly unpredictable. For example, E318A (negatively charged amino acid replaced by small hydrophilic residue) and E318K (negatively charged amino acid replaced by positively charged amino acid residue) both show essentially no change in binding to any FcγR. There are a number of additional examples within Presta to illustrate that this reference directly teaches the unpredictability of making amino acid changes.

In addition, as noted above, the Examiner has pointed to col. 12 to support the position that amino acid substitutions are interchangeable. As outlined above, this exact position by this same Examiner was rejected in the *Ex parte Watkins* (non-precedential) case. In *Watkins*, while the basis of the rejection was 102(e), the point made is identical; the Board rejected the Examiner's reliance on *Presta's* definition of amino acid substitution which lists twenty standard amino acids, because such definition "does not describe

substituting the amino acid at position 280 with any of these twenty amino acids." *Watkins* at 6. Moreover, the Board states:

> [W]e do not agree that Presta provides a specific teaching of substituting the amino acid at position 280 with each of these twenty amino acids and therefore with the three amino acids recited in claim 1. *Id.* at 6.

Further, Appellants note that alanine is described as hydrophobic. None of the specifically recited substitutions claimed by Appellants are hydrophobic. Therefore one skilled in the art would not be taught to substitute a variant claimed by Appellants. Presta states that the elected substitution is acidic. The 20 amino acids have very different chemical characteristics and cannot be simply substituted one for another. Thus, the teachings in Presta either teach away from the substitution of D (or any of the other amino acids) or alternatively in no way suggest it based on the very different chemical characteristics of naturally occurring S or substituted A.

Accordingly, even assuming, *arguendo*, that a prima facie case was made, the Appellants submit that these rebuttal arguments, in line with the Federal Circuit and Supreme Court positions on obviousness, render the claims patentable over Presta, whether the claims include functional language or not. As such, Appellants request that the rejection be withdrawn.

***III.*** *Obviousness-Type Double patenting*

A. Claims 88, 89, 103-106, 108, 109, 111, 112, 135-137, 139, 140, 142 and 144

Claims 88, 89, 103-106, 108, 109, 111, 112, 135-137, 139, 140, 142 and 144 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over the following copending applications:

Claims 1, 2, 10, 13, 17 and 18 of copending USSN 11/124,620,

Claims 9-12 and 19 of copending USSN 11/396,495,

Claims 1-5, 7-13, 20 and 21 of copending USSN 11/538, 406,

Claims 1-5, 8-13, 15, 20 and 21 of copending USSN 11/538,411,

Claims 1, 4-17 and 20-24 of copending USSN 11/544,165,

Claims 1, 3, 5, 6, 9 and 11-13 of copending USSN 11/765,402,

Claims 2, 13-17 and 38 of copending USSN 11/618,457,

Claims 2, 13-17 and 38 of copending USSN 11/618,472,

Claims 2, 13-17 and 38 of copending USSN 11/618,488,

Claims 1, 3, 5, 6, 9 and 11-13 of copending USSN 11/764,001,

Claims 1, 3, 5, 6, 9 and 11-13 of copending USSN 11/765, 353,

Claims 1, 3, 5, 6, 9 and 11-13 of copending USSN 11/765, 390,

Claims 1, 3, 5, 6, 9 and 11-13 of copending USSN 11/765, 402,

Claims 1, 3, 5, 6, 9 and 11-13 of copending USSN 11/766,609.

The present application was filed September 26, 2003. All of the above applications were filed after September 26, 2003. As noted in MPEP 804

> If a "provisional" nonstatutory obviousness-type double patenting (ODP) rejection is the only rejection remaining in the earlier filed of the two pending applications, while the later-filed application is rejectable on other grounds, the examiner should withdraw that rejection and permit the earlier-filed application to issue as a patent without a terminal disclaimer. If the ODP rejection is the only rejection remaining in the later-filed application, while the earlier-filed application is rejectable on other grounds, a terminal disclaimer must be required in the later-filed application before the rejection can be withdrawn.

In view of the arguments herein, Appellants submit that the provisional double patenting rejection should be the only remaining rejection of these claims. As the instant application was filed prior to any of the applications forming the basis of the provisional obviousness-type double patenting rejection, Appellants request that the rejection be withdrawn.

***IV.*** *Relief Requested*

Appellants have shown that that the withdrawal of claims 90-92, 94-102, 107 and 141 is in error. Appellants request that these claims be rejoined and examined with the remaining, pending claims.

Appellants have shown that the rejections under 35 USC 103(a) over Presta cannot be maintained because the Examiner has failed to make a

proper factual determination according to the *Graham* factors and has not provided a proper reason why the claimed invention as a whole is obvious in view of this reference. The Examiner has thus failed to establish a *prima facie* case of obviousness.

Appellants therefore respectfully request that the rejection of Claims 88, 89, 103-106, 108, 109, 111, 112, 135-137, 139, 140, 142 and 144 over Presta be withdrawn and that Claims 88, 89, 103-106, 108, 109, 111, 112, 135-137, 139, 140, 142 and 144, as well as Claims 90-92, 94-102, 107,141, 110 and 143 be allowed.

Appellants have shown that the obviousness-type double patenting rejections of Claims 88, 89, 103-106, 108, 109, 111, 112, 135-137, 139, 140, 142 and 144 are in error. Appellants request that the obviousness-type double patenting rejections be withdrawn and the claims be allowed.

Authorization is granted to charge any outstanding fees due at this time for the continued prosecution of this matter to Morgan, Lewis & Bockius LLP Deposit Account No. 50-0310 (Client-Matter No. 067461-5121-US). In the unlikely event that the fee transmittal or other papers are separated from this document and/or other fees or relief are required, Appellants petition for such relief, including extensions of time, and authorize the Commissioner to charge any fees under 37 CFR 1.16, 1.17 and 1.21 which may be required by this paper, or to credit any overpayment, to deposit account number 50-0310, order no. 067461-5121-US.

Respectfully submitted,

MORGAN LEWIS & BOCKIUS LLP

Date: 2/16/10

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# CLAIMS APPENDIX

## Listing of Claims

1 - 87. (Cancelled)

88. (Previously Presented) An antibody or immunoadhesin, said antibody or immunoadhesin comprising an amino acid substitution selected from the group consisting of 239D, 239E, 239Q, and 239T, wherein said antibody or immunoadhesin increases binding affinity to an FcγR as compared to its parent antibody or immunoadhesin, and wherein numbering is according to the EU index.

89. (Previously Presented) An antibody or immunoadhesin, said antibody or immunoadhesin comprising an amino acid substitution selected from the group consisting of 239D, 239E, 239N, 239Q, 239F, 239T, 239H and 239Y, wherein numbering is according to the EU index.

90. (Previously Presented) An antibody or immunoadhesin, said antibody or immunoadhesin comprising an amino acid substitution from the group consisting of 239D, 239E, 239Q, and 239T, wherein said antibody or immunoadhesin further comprises an amino acid substitution at a position selected from the group consisting of 234, 235, 240, 241, 243, 244, 245, 247, 256, 262, 263, 264, 265, 266, 267, 269, 270, 290, 296, 297, 298, 299,

312, 313, 322, 325, 326, 327, 328, 329, 330, 331, 332, 333, 334 and 339, wherein said antibody or immunoadhesin increases binding affinity to an FcγR as compared to its parent antibody or immunoadhesin, wherein numbering is according to the EU index.

91. (Previously Presented) An antibody or immunoadhesin of a parent Fc polypeptide, said antibody or immunoadhesin comprising an amino acid substitution selected from the group consisting of 239D, 239E, 239N, 239Q, 239F, 239T, 239H and 239Y, wherein said antibody or immunoadhesin further comprises an amino acid substitution at a position selected from the group consisting of 234, 235, 240, 241, 243, 244, 245, 247, 256, 262, 263, 264, 265, 266, 267, 269, 270, 290, 296, 297, 298, 299, 312, 313, 322, 325, 326, 327, 328, 329, 330, 331, 332, 333, 334 and 339, wherein numbering is according to the EU index.

92. (Previously Presented) An antibody or immunoadhesin-of a parent Fc polypeptide, said antibody or immunoadhesin comprising an amino acid substitution selected from the group consisting of of 239D, 239E, 239N, 239Q, 239F, 239T, 239H and 239Y, wherein said antibody or immunoadhesin further comprises an amino acid substitution at position 332, wherein numbering is according to the EU index.

93. (Cancelled)

94. (Previously Presented) An antibody or immunoadhesin according to claim 92 wherein said substitution at position 332 is selected from the group consisting of I332D, I332E, I332N, I332Q, I322T, I332H, I332Y, and I332A.

95. (Previously Presented) An antibody or immunoadhesin according to claim 92 comprising the amino acid substitutions 239D and 332E.

96. (Previously Presented) An antibody or immunoadhesin-of a parent Fc polypeptide, said antibody or immunoadhesin comprising an amino acid substitution at position 239 selected from the group consisting of 239D, 239E, 239Q, and 239T, wherein said antibody or immunoadhesin further comprises an amino acid substitution selected from the group consisting of 234D, 234E, 234N, 234Q, 234T, 234H, 234Y, 234I, 234V, 234F, 235D, 235S, 235N, 235Q, 235T, 235H, 235Y, 235I, 235V, 235F, 240I, 240A, 240T, 240M, 241W, 241L, 241Y, 241E, 241R, 243W, 243L, 243Y, 243R, 243Q, 244H, 245A, 247V, 247G, 262I, 262A, 262T, 262E, 263I, 263A, 263T, 263M, 264L, 264I, 264W, 264T, 264R, 264F, 264M, 264Y, 264E, 265G, 265N, 265Q, 265Y, 265F, 265V, 265I, 265L, 265H, 265T, 266I, 266A, 266T, 266M, 267Q, 267L, 269H, 269Y, 269F, 269R, 296E, 296Q, 296D, 296N, 296S, 296T, 296L, 296I, 296H, 297S, 297D, 297E, 298H, 299I, 299L, 299A, 299S, 299V, 299H, 299F, 299E, 313F, 325Q, 325L, 325I,

325D, 325E, 325A, 325T, 325V, 325H, 327N, 327L, 328M, 328D, 328E, 328N, 328Q, 328F, 328I, 328V, 328T, 328H, 328A, 329F, 330L, 330Y, 330V, 330I, 330F, 330R, 330H, 332D, 332E, 332N, 332Q, 322T, 332H, 332Y, and 332A, wherein numbering is according to the EU index.

97. (Previously Presented) An antibody or immunoadhesin of a parent Fc polypeptide, said antibody or immunoadhesin comprising an amino acid substitution selected from the group consisting of 239D, 239E, 239N, 239Q, 239F, and 239T, 239H and 239Y, wherein said antibody or immunoadhesin further comprises an amino acid substitution selected from the group consisting of 234D, 234E, 234N, 234Q, 234T, 234H, 234Y, 234I, 234V, 234F, 235D, 235S, 235N, 235Q, 235T, 235H, 235Y, 235I, 235V, 235F, 240I, 240A, 240T, 240M, 241W, 241L, 241Y, 241E, 241R, 243W, 243L, 243Y, 243R, 243Q, 244H, 245A, 247V, 247G, 262I, 262A, 262T, 262E, 263I, 263A, 263T, 263M, 264L, 264I, 264W, 264T, 264R, 264F, 264M, 264Y, 264E, 265G, 265N, 265Q, 265Y, 265F, 265V, 265I, 265L, 265H, 265T, 266I, 266A, 266T, 266M, 267Q, 267L, 269H, 269Y, 269F, 269R, 296E, 296Q, 296D, 296N, 296S, 296T, 296L, 296I, 296H, 297S, 297D, 297E, 298H, 299I, 299L, 299A, 299S, 299V, 299H, 299F, 299E, 313F, 325Q, 325L, 325I, 325D, 325E, 325A, 325T, 325V, 325H, 327N, 327L, 328M, 328D, 328E, 328N, 328Q, 328F, 328I, 328V, 328T, 328H, 328A,

329F, 330L, 330Y, 330V, 330I, 330F, 330R, 330H, 332D, 332E, 332N, 332Q, 322T, 332H, 332Y, and 332A, wherein numbering is according to the EU index.

98. (Previously Presented) An antibody or immunoadhesin according to claim 88 or 89 which is selected from the group consisting of 239E/332E, 239Q/332E, 239E/265G, 239E/265N, 239E/265Q, 239D/332D, 239D/332E, 239D/332N, 239D/332Q, 239E/332D, 239E/332N, 239E/332Q, 239N/332D, 239N/332E, 239N/332N, 239N/332Q, 239Q/332D, 239Q/332N, 239Q/332Q, 239E/264I/332E, 239Q/264I/332E, 239E/264I/330Y/332E, 239E/264I/298A/330Y/332E, 239D/297D/332E, 239E/297D/332E, 239D/265V/297D/332E, 239D/265I/297D/332E, 239D/265L/297D/332E, 239D/265F/297D/332E, 239D/265Y/297D/332E, 239D/265H/297D/332E, 239D/265T/297D/332E, 239N/330Y/332E, 239D/330L/332E, 239N/330L/332E, 264I/298A/332E, 239D/298A/332E, 239N/298A/332E, 239D/264I/332E, 239D/264I/298A/332E, 332E/239D/298A, 239D/330Y/332E and 239D/264I/330L/332E.

99. (Previously Presented) An antibody or immunoadhesin according to claim 98 which is 239D/332E.

100. (Previously Presented) An antibody or immunoadhesin according to claim 98 which is 239D/332E/330Y.

101. (Previously Presented) An antibody or immunoadhesin according to claim 98 which is 239D/332E/330L.

102. (Previously Presented) An antibody or immunoadhesin according to claim 98 which is 239D/332E/298A.

103. (Previously Presented) An antibody or immunoadhesin of a parent Fc polypeptide, said antibody or immunoadhesin comprising an amino acid substitution selected from the group consisting of 239D, 239E, 239N, 239Q, 239F, and 239T, 239H and 239Y, wherein said antibody or immunoadhesin increases binding affinity to an FcγR as compared to said its parent polypeptide antibody or immunoadhesin, wherein numbering is according to the EU index.

104. (Previously Presented) An antibody or immunoadhesin according to claim 103 wherein said FcγR is FcγRIIIa.

105. (Previously Presented) An antibody or immunoadhesin according to claim 104 wherein said FcγRIIIa is a V158 or F158 allotype of FcγRIIIa.

106. (Previously Presented) An antibody or immunoadhesin according to any of claims 88-92 and 96-97 wherein said substitution is 239D.

107. (Previously Presented) An antibody or immunoadhesin according to any of claims 88-92 and 96-97 wherein said substitution is 239E.

108. (Previously Presented) An antibody or immunoadhesin according to any of claims 88-92 and 96-97 wherein said antibody or immunoadhesin is an antibody.

109. (Previously Presented) An antibody according to claim 108 wherein said antibody is selected from the group consisting of a human antibody, a humanized antibody, and a monoclonal antibody.

110. (Withdrawn – Previously Presented) An antibody or immunoadhesin according to any of claims 88-92 and 96-97 wherein said antibody or immunoadhesin further comprises an engineered glycoform.

111. (Previously Presented) An antibody or immunoadhesin according to any of claims 88-92 and 96-97 wherein said antibody or immunoadhesin has specificity for a target antigen selected from the group consisting of CD19, CD20, CD22, CD30, CD33, CD40, CD40L, CD52, Her2/neu, EGFR, EpCAM, MUC1, GD3, CEA, CA 125, HLA-DR, TNFalpha, MUC18, prostate specific membrane antigen (PMSA) and VEGF.

112. (Previously Presented) A composition comprising the antibody or immunoadhesin according to any of claims 88-9392 and 96-97 further comprising a pharmaceutically acceptable carrier.

113 to 134 (Canceled)

135. (Previously Presented) An antibody or immunoadhesin comprising a 239D amino acid substitution, wherein said numbering is according to the EU index.

136. (Previously Presented) An antibody or immunoadhesin comprising a 239E amino acid substitution, wherein said numbering is according to the EU index.

137. (Previously Presented) An antibody or immunoadhesin according to claim 135 or 136 wherein said antibody or immunoadhesin increases binding affinity to an FcγR as compared to its parent antibody or immunoadhesin.

138. (Canceled)

139. (Previously Presented) A protein comprising an Fc variant of a parent Fc polypeptide comprising an amino acid modification in the Fc region of said parent Fc polypeptide selected from the group consisting of 239D and 239E, wherein said protein increases binding affinity to an FcγR as compared to said parent Fc polypeptide, wherein numbering is according to the EU index.

140. (Previously Presented) A protein comprising an Fc variant of a parent Fc polypeptide comprising an amino acid modification in the Fc region of

said parent Fc polypeptide, selected from the group consisting of 239D and 239E, wherein numbering is according to the EU index.

141. (Previously Presented) A protein comprising an Fc variant of a parent Fc polypeptide comprising an amino acid modification in the Fc region of said parent Fc polypeptide selected from the group consisting of 239D, 239E, 239N, 239Q, 239F, 239T, 239H and 239Y, wherein said protein further comprises an amino acid substitution at position 332, wherein numbering is according to the EU index.

142. (Previously Presented) A protein according to claim 139, 140 or 141 wherein said protein is an antibody.

143. (Previously Presented) A protein according to claim 142 wherein said antibody further comprises an engineered glycoform.

144. (Previously Presented) A composition comprising the protein of claim 139, 140, 141 or 143 further comprising a pharmaceutically acceptable carrier.

# EVIDENCE APPENDIX

None

# RELATED PROCEEDINGS APPENDIX

None